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# **Novel anticoagulants in the therapy of peripheral arterial and coronary artery disease**

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**Key words:** Atherothrombosis, new oral anticoagulants, antithrombotic therapy, peripheral arterial disease, coronary artery disease

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## **Abstract**

Anticoagulant and antiplatelet drugs are used and studied in numerous trials for primary and secondary prevention of atherothrombosis since decades. The annual rate for cardiovascular morbidity and mortality is high in patients following an acute coronary syndrome and in patients with peripheral arterial disease due to concomitant coronary and cerebrovascular diseases. Plaque rupture and subsequent thrombosis involves activation of both platelets and coagulation factors. Therefore the combination of aspirin and warfarin to improve prevention of atherothrombosis compared to antiplatelet therapy alone was studied but could not be established due to significantly increased risk of major bleeding compared to a non-significant reduction in ischemic events. During the past two decades, clinical trials focused on combined antiplatelet therapies in the prevention of secondary events following acute coronary syndromes and very recently on the new oral anticoagulants in combination with antiplatelet therapy. This review discusses the role the new oral anticoagulants such as Factor IIa (thrombin) and Factor Xa inhibitors in atherothrombosis, their pharmacological properties and recently published clinical data in secondary prevention of atherothrombotic events and potential implications for patients with peripheral arterial disease.

**Key words:** atherothrombosis, new oral anticoagulants, antithrombotic therapy, peripheral arterial disease, coronary artery disease

## **Highlights**

- Peripheral and coronary artery disease has a high ischemic event rate despite antiplatelet therapy.
- Antiplatelet and anticoagulant agents inhibit different pathways of the coagulation pathway.
- Combination of antiplatelet agents with novel oral Factor II or Factor X inhibitors may reduce ischemic events.
- Combined antithrombotic therapy must carefully be tested for antithrombotic benefits and bleeding risk.

## Introduction

Atherothrombosis is defined by the occurrence of both atherosclerosis and thrombosis in an artery and results in myocardial, cerebral, limb and reno-mesenteric ischemia (1-4). Amongst the atherosclerotic diseases, patients with peripheral arterial disease (PAD) have an extensively large atherosclerotic burden, often coexisting coronary (CAD) and cerebrovascular disease, and have three times as high as the risk of myocardial infarction or stroke as patients without PAD (3, 5). Likewise, recurrent ischemic events are as high as 10% per annum following in acute coronary syndrome (6, 7) . Despite antiplatelet therapy, up to 10-20% of these patients still have cardiovascular events, indicating that the underlying atherothrombotic activity is not optimally controlled by antiplatelet agents. Therefore, the combination of antiplatelet therapy with oral anticoagulants to reduce atherothrombotic events has been studied in the Warfarin Antiplatelet Vascular Evaluation trial (WAVE) for patients with PAD (8, 9). This trial showed a non-significant reduction in ischemic events but a significant increase in bleeding complications (RR 3.41; 95% CI, 1.84-6.35) during an observation period of 35 months. The bleeding risk under combined antiplatelet and anticoagulant therapy is higher in PAD than in CAD without PAD. This might be attributable to different factors such as older age, vascular fragility and higher morbidity (10, 11). However, the combined antithrombotic therapy is not recommended for atherothrombosis in general (12) .

Currently in the dawn of a new anticoagulant era with numerous new anticoagulant drugs that have either specific anti-thrombin or anti-FXa activity- compared to Vitamine K antagonists, that interfere in multiple ways in the coagulation cascade- more numerous trial for prevention and therapy of venous thromboembolism, prevention of embolic complication due to atrial fibrillation and therapy of atherothrombosis are reported and upcoming (13).

Besides the afore mentioned increased risk of bleeding when combining antiplatelet drugs with Vitamin K antagonists, their narrow therapeutic windows, need for frequent laboratory

monitoring, food and drug interactions poses several disadvantages. The development of novel oral factor Xa inhibitors and oral direct thrombin inhibitors provide an alternative to vitamin K antagonists. In this paper, we discuss the new agents, rivaroxaban, apixaban, and dabigatran, for secondary prevention of acute atherothrombosis and their therapeutic potential for patients with PAD and CAD.

### **Atherothrombosis and ischemia**

Thrombosis plays a critical role in the pathomechanism of ischemic syndromes, as disruption of an atherosclerotic plaque exposes blood to subendothelial collagen, tissue factor, and other procoagulant molecules such as thrombin that trigger activation of platelets and formation of fibrin within the vessel lumen (14-16). Endothelial damage and dysfunction as well as inflammation and coagulation are closely related to the pathophysiology of ischemic syndromes (17). Platelets play key roles in both the formation of the atheromatous plaque and clinical presentation of acute atherothrombotic events following plaque rupture. In the pathogenesis of atherothrombosis, clotting activation has a crucial role and thrombin generation is involved both platelet activation and fibrin (Figure 1.).

In animal models, hypercoagulability tends to increase atherosclerosis, whereas hypocoagulability reduces the atherosclerotic burden (18). If this direct relationship between coagulation and atherosclerosis applies for humans is not clear. Almost all coagulation proteins, including tissue factor, are found in atherosclerotic lesions in humans. In addition to generating local fibrin, an environment for cell growth, serine proteases such as thrombin are thought to be involved in cell signaling processes, acting through the activation of protease-activated receptors (17). Activation of such protease-activated receptors on vascular cells triggers other complex processes promoting atherosclerosis, including inflammation, angiogenesis, and cell proliferation.

Direct thrombin inhibitors and anti-FXa-inhibitors are targeting at this crucial phase of

thrombin generation with the potential to prevent thrombosis and progression of atherosclerosis alike. Therefore, the novel anticoagulants may have synergistic antithrombotic and bleeding balance due to their pharmacodynamic and pharmacokinetic properties which combined with antiplatelet agents may improve overall net effects. Furthermore, combined therapy may be of benefit in aspirin resistance, which is both a clinical and laboratory problem (s. Kasmeridis, Apostollakis, Lip: Aspirin and Aspirin Resistance in Coronary Syndrome, in this issue of Current Opinion in Pharmacology).

### **Novel anticoagulants**

In comparison to oral Vitamine K antagonist, either direct inhibitors of thrombin or factors Xa have overall favorable pharmacological effects . Examples of direct factor Xa inhibitors include apixaban, rivaroxaban, otamixaban, betrixaban and edoxaban. Direct thrombin inhibitors (factor IIa inhibitors) were developed with the limitations of standard heparin and warfarin in mind. Examples include ximelagatran, argatroban, and dabigatran etexilate. In common for these novel anticoagulants is the convenience of use with no requirement for laboratory monitoring and limited drug interactions, which may provide multifaceted treatment options for atherosclerosis and anticoagulation in the future (13). Due to the data available, this review discusses the two anti- Factor X inhibitors, rivaroxaban and apixaban, and the oral thrombin inhibitor dabigatran etexilate (Table 1)(19-22). There are differences between Factor Xa and thrombin that may cause these clotting factors to be affected differently by drugs that inhibit them. Currently, the only known functions of Factor Xa are promotion of coagulation and inflammation (23). Thrombin has more diverse actions in the body; in addition to its known effects on coagulation and inflammation, thrombin also activates protein C (which has anticoagulant properties) and promotes cellular proliferation .

### ***Rivaroxaban***

Rivaroxaban is a direct factor Xa inhibitor with high and high plasma protein binding (92–95%). In a concentration-dependent manner, rivaroxaban inhibits free factor Xa and prothrombinase-bound and clot-associated factor Xa. As a consequence, rivaroxaban prevents thrombin generation by inhibiting factor Xa generated via both the intrinsic and extrinsic coagulation pathways [4] but does not exhibit direct effect on platelet aggregation induced by collagen, adenosine diphosphate or thrombin (24).

The pharmacokinetic profile of rivaroxaban shows favorable safety and tolerability profile. The bioavailability of a 10 mg dose of rivaroxaban is high (80–100%), and rivaroxaban is rapidly absorbed, reaching a maximal plasma concentration (C<sub>max</sub>) within 2–4 h after oral administration (Table 1). Rivaroxaban displays near linear pharmacokinetics, with a half-life of 7–11/11–13 h (for young/elderly subjects) and no significant accumulation after repeat dosing (ceiling effect). The pharmacokinetic profile is unaffected by food or antacids. Furthermore, there is no inhibition or induction of cytochrome-P-450 (CYP450) isoforms. Rivaroxaban is eliminated in two-thirds through metabolic degradation in the liver, half of which is excreted via the kidneys and half via the hepatobiliary route. One-third of the dose is eliminated as unchanged drug in the urine. There are no active circulating metabolites of rivaroxaban.

### ***Apixaban***

Apixaban, like rivaroxaban, interrupts the coagulation cascade by blocking the enzymatic activity of Factor Xa (25, 26). Apixaban is a direct inhibitor of factor Xa. Orally administered apixaban reaches a bioavailability of 50% and C<sub>max</sub> is 3–4 hours (Table 1). The half-life is 10–14 h after repeated doses. Apixaban is metabolized in part by CYP3A4; it is partly eliminated by the kidneys (25%) and, to some extent, also processed via CYP-independent mechanisms in the liver. Similarly to rivaroxaban, apixaban does not induce or inhibit CYP enzymes and has a low likelihood of drug-drug or food-drug interactions.



### ***Dabigatran etexilate***

Dabigatran directly inhibits both free and clot-bound thrombin. Dabigatran etexilate (a pro-drug) is rapidly converted (after oral administration and hepatic processing) to dabigatran, with C<sub>max</sub> after 1.5 h after oral ingestion (Table 1). Dabigatran has a half-life of 14 -17 hours at steady state. In contrast to rivaroxaban, bioavailability is low with only 7.2%, and therefore it is predominantly excreted in the feces. Although part of the bioconversion from pro-drug to active metabolite occurs in the liver, the CYP450 system is not involved. Potentially important drug interactions with quinine/quinidine and verapamil have been described. After hepatic activation, 80% of dabigatran is eliminated in the kidneys; thus, as for rivaroxaban and apixaban, patients with severe renal impairment have been excluded from most clinical trials.

### **Clinical data for the novel oral anticoagulants in acute atherothrombosis**

All three novel oral anticoagulants have been evaluated in clinical trials for prevention of primary or secondary venous thromboembolism, and non-valvular atrial fibrillation and in addition for secondary prevention of atherothrombosis following acute coronary syndromes (phase III trials only for rivaroxaban and apixaban). Table 2 compares antithrombotic effects and bleeding risk of different trials with new antiplatelet and anticoagulant agents.

### ***Rivaroxaban***

Rivaroxaban has been approved for the prevention primary or recurrent venous thromboembolism as well as for prevention of systemic embolization in non-valvular atrial fibrillation (27-29). However, the indication for prevention of recurrence of atherothrombosis was rejected July 2012 by the Food and Drug Administration due to increased bleeding risk in

patients with a recent acute coronary syndrome although rivaroxaban reduced the risk of the composite end point of death from cardiovascular causes, myocardial infarction, or stroke (19). Rivaroxaban increased the risk of major bleeding and intracranial hemorrhage but not the risk of fatal bleeding. In ATLAS ACS 2-TIMI 51, a double-blind, placebo-controlled trial published early in 2012, approximately 15'000 patients with a recent acute coronary syndrome received twice-daily doses of either 2.5 mg or 5 mg of rivaroxaban or placebo in addition to aspirin/clopidogrel (81% of patients with dual agents) for a mean of 13 months. The trials' primary efficacy end point was a composite of death from cardiovascular causes, myocardial infarction, or stroke. Primary end point was 8.9% for rivaroxaban and 10.7% for placebo (hazard ratio 0.84; 95% confidence interval , 0.74 to 0.96;  $p=0.008$ ), with significant improvement for both the twice-daily 2.5-mg dose (9.1% vs. 10.7%,  $p=0.02$ ) and the twice-daily 5-mg dose (8.8% vs. 10.7%,  $p=0.03$ ). Remarkably, the twice-daily 2.5-mg dose of rivaroxaban reduced the rates of death from cardiovascular causes (2.7% vs. 4.1%,  $p=0.002$ ) and from any cause (2.9% vs. 4.5%,  $p=0.002$ ). In contrast, this survival benefit that was not achieved with the twice-daily 5-mg dose. As compared with placebo, rivaroxaban increased the rates of major bleeding (2.1% vs. 0.6%,  $p<0.001$ ) and intracranial hemorrhage (0.6% vs. 0.2%,  $p=0.009$ ), without a significant increase in fatal bleeding (0.3% vs. 0.2%,  $p=0.66$ ) or other adverse events. The twice-daily 2.5-mg dose resulted in fewer fatal bleeding events than the twice-daily 5-mg dose (0.1% vs. 0.4%,  $p=0.04$ ).

The striking finding of ATLAS ACS 2-TIMI 51 is that the survival benefit for rivaroxaban was only observed with the 2.5-mg twice-daily dose, one quarter of the dose studied in atrial fibrillation or venous thromboembolism, but again suggesting that higher doses may offset the benefit with more bleeding events.

### ***Apixaban***

The APPRAISE-2 trial (apixaban after acute coronary syndromes) contrasts the ATLAS ACS

2-TIMI 51 since it was stopped early due to a highly significant increase in major bleeding without any relevant reduction in ischemic events (30). Only after a median follow-up of 241 days, the primary outcome of cardiovascular death, myocardial infarction, or ischemic stroke occurred 7.5% assigned to apixaban and in 7.9% assigned to placebo (hazard ratio with apixaban, 0.95; 95% confidence interval, 0.80 to 1.11; p=0.51). The primary safety outcome of major bleeding occurred in 1.3% who received apixaban and in 0.5% with placebo (hazard ratio with apixaban, 2.59; 95% confidence interval, 1.50 to 4.46; p=0.001). A greater number of intracranial and fatal bleeding events occurred with apixaban than with placebo (0.3/0.1 % vs. 0.1/0 %).

### ***Dabigatran etexilate***

There is only dose findings study (phase II) for the oral direct thrombin inhibitor dabigatran etexilate (RE-DEEM) (31-33). In the RE-DEEM trial, with almost all patients receiving dual platelet inhibition, a dose-dependent increase in clinically relevant bleeding events was observed, with highest rates with the dabigatran etexilate 110 mg and 150 mg twice daily as currently used in atrial fibrillation. The most frequently reported bleeding events were gastrointestinal bleeding and epistaxis. The study was not powered to demonstrate an efficacy difference in cardiovascular death, nonfatal myocardial infarction or nonhemorrhagic stroke, but a numerically lower proportion was attained in the 2 higher dabigatran doses (110 mg twice daily., 3.0%; 150 mg twice daily., 3.5%) compared with the lower doses (50 mg twice daily., 4.6%; 75 mg twice daily., 4.9%) and the placebo group (3.8%).

### ***Other emerging anticoagulants***

Darexaban, another Factor IIa Inhibitor, was evaluated for safety and tolerability for the prevention of ischemic events in acute coronary syndromes (34). Darexaban, when added to dual antiplatelet therapy, produced a dose-related 2- to 4-fold increase in bleeding versus

placebo, with no other safety concerns, but also with no efficacy.

### **Discussion:**

There are two new oral anticoagulant drugs with phase III studies that were conducted for secondary prevention of atherothrombotic events (The APPRAISE-2 trial and ATLAS ACS 2–TIMI 51) - of which the APPRAISE was prematurely terminated because of an excess of bleeding with apixaban and no evidence of benefit (19, 30). There was no phase III trial for dabigatran based on similar issues following the phase II study and on findings suggesting an increased risk of myocardial ischemia (33). Only the ATLAS ACS 2–TIMI 51 met its primary objective but also with a three to four fold increase in intracranial bleedings (31).

This difference between APPRAISE-2 and ATLAS ACS 2 TIMI 51 is not well explained by different bleeding rates, which was increased to a similar extent in both trials. The APPRAISE-2 population was older and more commonly, had diabetes, renal insufficiency, and history of stroke, and more severe myocardial ischemia (32). The higher risk population included in the APPRAISE-2 study was reflected by a higher rate of the primary efficacy outcome. This may be attributable to a different pathophysiology—and eventually be less related to thrombotic events and thereby less responsive to anticoagulant treatment—than in the ATLAS-2 trial. In addition, FXa inhibition potency of the studied doses was different: APPRAISE-2 used the same 5 mg twice daily apixaban dose tested in atrial fibrillation, whereas ATLAS-2 used 2 doses ( 2.5 mg/ 5 mg twice daily), that were one fourth to one half of the total daily dose of rivaroxaban (20 mg once daily) tested in atrial fibrillation. This might hypothetically suggest that a lower, rather than a higher, level of FXa inhibition per se may have a better antithrombotic effect.

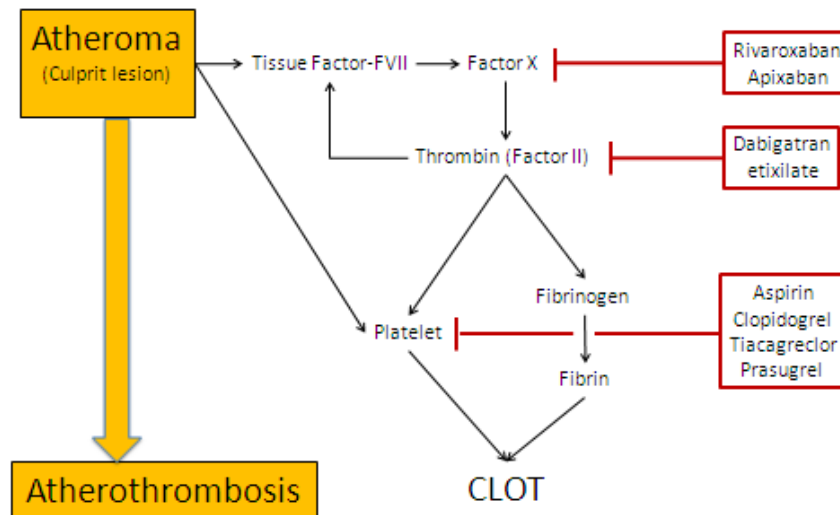
Taken together, the combination of a dual antiplatelets therapy with a novel oral anticoagulant is associated with dose-dependent increased risk for major and intracranial bleeding risk and only with rivaroxaban with a significantly lower rate of ischemic related deaths. Although

the American Food and Drug administration did not approve rivaroxaban for secondary prevention of acute coronary syndrome, ATLAS ACS 2-TIMI 51 provides evidence that reduction of the persistently high morbidity and mortality after myocardial ischemia is possible (Figure 2). So far, combination of antithrombotic therapy has shifted the ischemic-bleeding balance in a parabolic function with slightly lower recurrent atherothrombosis but higher risk for major bleeding, or vice versa. Nevertheless, the combination of only one antiplatelet agent (aspirin) with one new oral anticoagulant - of which rivaroxaban at a dosage of 2.5 mg twice daily seems to be the candidate- might be tempting for patient with PAD. In contrast to patients with a recent acute coronary syndrome, patients with PAD at a chronic stage are not treated by dual antiplatelets drugs irrespective of their risk for atherothrombotic events. Therefore, a logic consequence would be a trial -similar to the WAVE study (warfarin and aspirin) - with aspirin and low dose rivaroxaban (8). With regard to the high incidence of atherothrombotic events in this atherosclerotic subgroup, an improved therapy for secondary prevention is still needed for PAD. The main safety issue with bleeding risk will jeopardize the potential antithrombotic benefit, and patients with PAD are usually older and more fragile. Hence, PAD patients with previous cerebral ischemia or major bleedings should be evaluated with great caution. In contrast to WAVE trial with warfarin and a target international normalized ratio of 2.0 to 3.0, a trial with rivaroxaban 2.5mg combined with aspirin represents a lower bleeding risk, since 2.5mg of rivaroxaban is a quarter of the dosage that is used for atrial fibrillation.

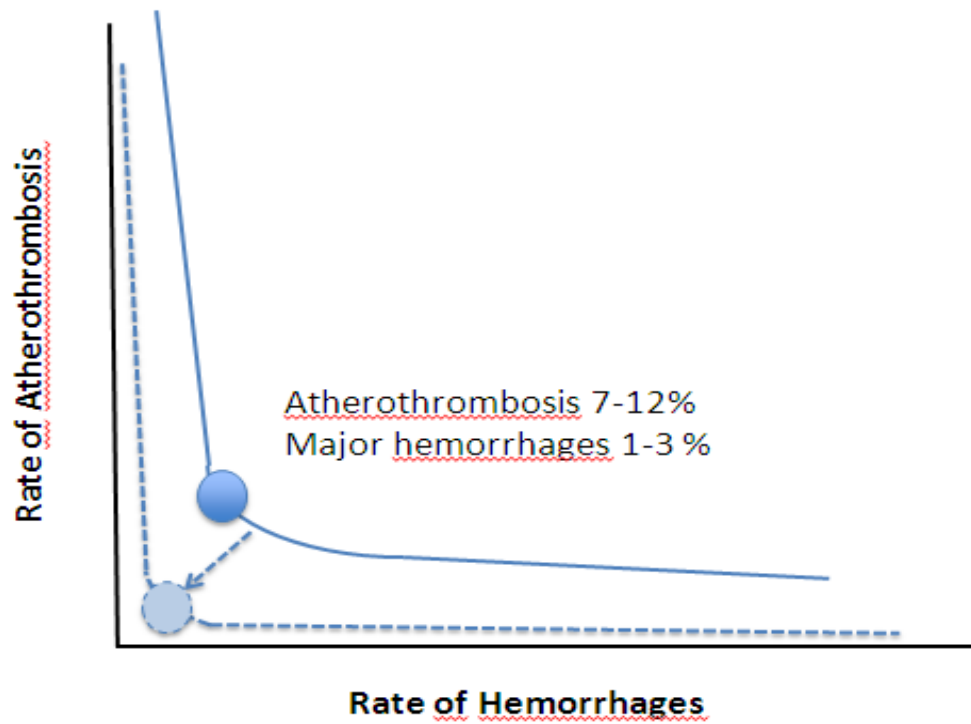
In conclusion, atherothrombosis is often insufficiently controlled by antiplatelet therapy alone. Combination of antiplatelet agents with novel anticoagulants may reduce ischemic events but is associated with an increased risk for major bleedings. So far, no novel anticoagulant drug is approved for secondary prevention following acute coronary syndrome. PAD patients are a fragile subgroup of atherosclerotic patients with substantial risk for atherothrombotic events and need to be carefully evaluated for combined antithrombotic therapy with the novel

anticoagulants.

## Legends



**Figure 1.** Simplified coagulation and clotting cascade in atherothrombosis and antithrombotic drug actions.



**Figure 2.** Rates of recurrent atherothrombotic and bleeding events in patients with symptomatic atherosclerosis. The parabolic function indicates that in dependence of antithrombotic agents the risk shifts towards either higher bleeding or higher ischemic risk. Ideally the shift should tend towards both lower ischemic and bleeding events (dotted line).

Table 1. Pharmacological properties of the new oral anticoagulants

	<u>Rivaroxaban</u>	<u>Dabigatran</u>	<u>Apixaban</u>
<u>Target molecule</u>	<u>Factor-Xa inhibitor</u>	<u>Factor-IIa inhibitor</u>	<u>Factor-Xa inhibitor</u>
<u>Half-life time (h)</u>	5–13	11–14	~12
<u>Maximal plasma concentration (C<sub>max</sub>) (h)</u>	2–4	0.5–2	1–3
<u>CYP450-metabolism</u>	<u>no</u>	<u>no</u>	<u>no</u>
<u>Food interaction</u>	<u>none</u>	<u>none</u>	<u>none</u>
<u>Pro-Drug</u>	<u>no</u>	<u>yes</u>	<u>no</u>
<u>Bioavailability (%)</u>	80–100	~3–8	~52
<u>Renal elimination (%)</u>	~33	~85	~27



Table 2. Ischemic and bleeding event rates in drug trials for peripheral arterial disease and acute coronary syndrome.

Event (%)	Peripheral arterial disease		Acute coronary syndrome						
	ASA	ASA+ Warfarin	Triton-TIMI 38		PLATO		APPRAISE-2		ATLAS ACS 2-TIMI 51
			Prasugrel	Clopidogrel	Ticagrelor	Clopidogrel	Apixaban	Placebo	Placebo Rivaroxaban (2.5mg)
Death, MI, Stroke	13.3	12.2	10.7	12.7	10.2	12.3	8.8	8.9	9.1
Death, MI, Stroke	17.4	15.9							
Limb ischemia									
Cardiovascular Death	6	6.1	2.1	2.4	4.0	5.1	2.8	3.0	2.7
Major Bleeding	*2.2	*6.9	2.4	1.8	2.8	2.2	1.3	0.5	1.8
Fatal Bleeding	0.3	0.9	0.4	0.1	0.3	0.3	0.1	0	0.1
Net Events	19.6	22.8	13.1	14.5	13.0	12.5	10.1	9.4	10.9
Net Deaths	6.3	7.0	2.5	2.5	4.3	5.4	2.9	3.0	2.8

† includes events up to 35 months, whereas comparator trials only up to 12 months.

\* includes moderate bleedings. Life threatening bleeding and fatal bleeding is 4.9 % for combined therapy and 1.5% for antiplatelet therapy adapted from

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